## REMARKS

Claims 1-10 and 121, 123-130 are pending. Claims 6 and 125 have been revised by incorporation of the elements of dependent claims 122 and 131 into these claims. No new matter has been added.

Anticipation Rejection

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

The Examiner has rejected claims 6-9 as anticipated by Kumar WO 00/71124. Claims 6-9 have been amended to add a trituration step which is not taught by Kumar. The amendment makes the rejection moot.

First Obviousness Rejection

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The Examiner rejects claims 1-10, 121-131 as obvious over Kumar and secondary references. According to the examiner, the difference between these claims "and the prior art spray drying process of obtaining amorphous fexofenadine hydrochloride is that the claims are limited to the particular solvent THF or evaporation process for solvent removal." The Applicants respectfully disagree. Claim 1 uses a combination of extraction and evaporation process. It is distinguishable from the prior art for reasons in addition of the differences in solvents. Claims 6 and 125 as amended use a trituration process to obtain amorphous fexofenadine hydrochloride. The prior art does not teach use of a trituration process to obtain amorphous fexofenadine hydrochloride.

The Examiner also states that "Okabe et al. CA 114 disclosed that both spray dryer and evaporator are alternative apparatus for solvent removal." Okabe is not a relevant reference since it prepares ceramic oxide for electric insulation.

The Examiner then states that "Williams et al. '890 taught that in pharmaceutical particulation processes of fexofenadine hydrochloride (see col. 15 line 39), spray drying is a solvent removal procedure analogous to other conventional solvent removing procedures (see col. 1 lines 26-27, .col. 2 lines 59-60) and optionally ethanol, methanol or tetrhydrokan are choices of solvents (see col. 4 lines 5 1-56)." Column 15 line 39 of Williams is a dependent claim that recites fexofenadine HCl as a laundry list of about 30 pharmaceuticals. It does not even state that the fexofenadine HCl is amorphous form. The other portions of Williams, Col. 1, lines 26-27 and .col. 2 lines 59-60, state that solvent removal may be carried out by lyophilization or freeze drying. There is no mention that the product obtained would be amorphous. Furthermore, the process of Williams is "spray freezing" which is different than the process of the present invention. Thus Williams is not relevant since it does not exemplify fexofenadine HCl, uses a different process than claimed and does not even mention that any process it discloses could be used to prepare amorphous form of any pharmaceutical, nevertheless that of fexofenadine HCl.

According to the Examiner, a prima facie case is made: "On having ordinary skill in the art in possession of the above references are in possession of the claims because Kumar et al. disclosed proven process of obtaining amorphous fexofenadine hydrochloride from solution by solvent removing and Williams or Okabe taught the proven interchangeability among the different solvents and solvent removing techniques conventional in the art."

The Applicants respectfully disagree. Kumar discloses use of spray drying. As the Examiner is aware spray drying is a technique where droplets of a solution are introduced into an apparatus that uses heated air circulating in the apparatus to dry the droplets (Like a hair dryer). Evaporation by spray drying is substantially different than the evaporations carried out by the present invention. With a spray drier seeding does not occur since the solution is introduced as droplets into the chamber and it turns into a solid before it is collected. But in evaporation without use of spray dryer, the evaporation may result in seeding of the solution by the first solids that form. Seeding of course is detrimental to preparation of amorphous form.

In claim 1, the Applicants invented a process which through dissolution in THF, followed by extraction with a hydrocarbon, and removal of the hydrocarbon results in amorphous fexofenadine HCl. The references cited do not teach or suggest that an amorphous form could be obtained by such combination of extraction and evaporation process. Furthermore, Kumar uses methanol/ethyl acetate, methanol/acetone, methanol/isopropanol and methanol as solvents. There is no teaching or suggestion that amorphous form could be obtained by evaporating a hydrocarbon, which hydrocarbon has substantially different properties than the solvent used by Kumar. Furthermore, there is no

teaching in Kumar or the other references that amorphous form could be obtained by a process that encompasses trituration.

Second Obviousness Rejection

According to the Examiner, "The primary references disclosed fexofenadine hydrochloride" and that "the difference between the prior art and the instant claims is that the amorphous form or process of spray dry or evaporation etc. for preparing an amorphous form was not explicitly disclosed. However, Lieberman, Suzuki, Corrigan, Nuernberg or Sato provided perponderous of evidence that spray drying or evaporation process are size reduction processes for pharmaceutical products and such size reduction would enhance drug dissolution thus bioavailability (see Lieberman)."

For the rejection in light of the second group of references, the Examiner equates size reduction techniques with preparation of amorphous form. For this proposition, the Examiner relies on an inherency theory: "One skilled in the art would be motivated to carry out the prior art process employing spray drying or evaporation since it was clearly suggested by the prior art that spray drying and evaporation are size reduction routine procedure in formulation which enhances drug dissolution, **also such process would inherently produce the amorphous form**."

First, the filed of polymorphism is unpredictable. The literature is replete with references attesting to the unpredictability of polymorphs. The process of crystallization is affected by many physical parameters, and this element of predictability has serious implications for solids design in crystal engineering. M. Caira, (Crystalline Polymorphism of Organic Compounds," *Topics in Current Chemistry*, vol. 198, 164-208 (1998). "There's no way to tell what a large floppy molecule can do in the solid state except by doing experiments." M. Rouhi, "The Right Stuff," Chem. & Eng. News 32-35 (2003). Because of this unpredictability, there is no basis for the proposition that a process for preparation of amorphous form with one pharmaceutical would invariably and necessarily produce amorphous form with another pharmaceutical.

Second none of the references cited are relevant to a showing of obviousness of the claimed subject matter. For example, Sato discloses preparation of amorphous solid of 9,3"-diacetylmidecamycin with freeze drying method and grinding process. Corrigan discloses the potential of spray drying to produce high energy drug forms using phenobarbitone. These references in addition to not disclosing fexofenadine HCl, do not teach or suggest that amorphous form of fexofenadine HCl could be obtained by the claimed processes. In claim 1, the Applicants invented a process which through dissolution in THF, followed by extraction with a hydrocarbon, and removal of the hydrocarbon results in amorphous fexofenadine HCl. The references cited do not teach or suggest that an amorphous form

could be obtained by such combination of extraction and evaporation process. Furthermore, there is no teaching or suggestion in Kumar or the other references that amorphous form could be obtained by a process that encompasses trituration.

Anticipation Rejection

With regard to the provisional anticipation rejection under 102(g), that section is only relevant either during the course of an interference (which is not the case here) or an invention by another in this country. The inventor listed on US2005/016056 is Swiss and it is unlikely that the claimed subject matter of the publication meets the "in this country" requirement of 102(g)(2). In regard to the rejection under Section 102(e), the 102(e) date of the publication is January 17, 2002 (as the Examiner is aware, a foreign priority application is not given a 102(e) date because it is not published). The present application claims the benefit of eight provisional applications before the January 17, 2002 date, at least some of which disclose the claimed subject matter. Therefore, US2005/016056 is not a 102(e) art.

Applicants thus submit that the entire application is now in condition for allowance, an early notice of which would be appreciated. Should the Examiner not agree with Applicants' position, a personal or telephonic interview is respectfully requested to discuss any remaining issues prior to the issuance of a further Office Action, and to expedite the allowance of the application.

Respectfully submitted,

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